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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,046	10/01/2001	Liang Xu	2444-105-I	8537

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ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,046	XU ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8,12,69 and 73-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 7, 8, 12, 69 and 73-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *attached hereto* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/30/06 has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group II (claims 1-4, 7, 8, 12, 69, 73, 74 and newly added claims 75 and 76), and species of immunoliposome comprising a pre-linked antibody fragment that binds a transferrin receptor and further comprises DNA encoding wild type p53 in Applicant's responses filed 8/27/04 and 4/30/04. Group I had been rejoined to Group II.

Claims 1-4, 7, 8, 12, 69 and 73-76 are currently being examined.

3. For the purpose of prior art rejections, the filing date of the instant claims 1-4, 7, 8, 12, 69 and 73-76 is deemed to be the filing date of PCT US00/04392, *i.e.,* 2/22/00, as the parent provisional application 60/121,133 does not support the claimed limitations of the instant application. The said limitations are those of the ratios recited at the last 3 lines of claim 1 and "MPB" in claim 8.

Applicant's comments in Applicant's amendment filed 3/30/06 are noted by the Examiner, however, Applicant has not pointed to support in the parent provisional application for limitations of the ratios recited at the last 3 lines of claim 1 and "MPB" in claim 8.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-4, 7, 8, 12, 69 and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2004/0209366 A1 (of record) in view of Spragg *et al* (PNAS USA 94: 8795-8800, 1997), Martin *et al* (J. Biol. Chem. 257(1): 286-288, 1982, of record), US 4,946,778, Wang *et al* (Bioconjugate Chemistry 8: 878-884, 1997, of record), Xu *et al* (Human Gene Therapy: 467-475, 1997, IDS reference) and U.S. Patent No. 6,200,956 B1 (of record).

US 2004/0209366 A1 discloses use of a targeting moiety such antibody fragments such as scFv or Fab' linked to an effector cationic lipid nucleic acid complex, *i.e.,* an immunoliposome loaded with an effector molecule, provides the ability to conveniently customize the complex for delivery to specific cells and tissues. US 2004/0209366 A1 discloses that the antibody may be attached to the liposome either before or after the formation of the nucleic acid:lipid complex. US 2004/0209366 A1 further discloses that an example of an effector is a nucleic acid molecule encoding a tumor suppressor gene such as p53 that can be specifically targeted to cells such as cancer cells using a targeting moiety. US 2004/0209366 A1 discloses that for *in vivo* applications, cholesterol is used as a helper lipid, whereas for *in vitro* applications, DOPE is used as a helper lipid. US 2004/0209366 A1 discloses that the ratio of DNA to lipid is 1 ug/8-12 nmol, and the ratio of antibody to lipid is 15.6 ug of scFv to 1 umol lipid, or on a w:w basis 1:14 which is in the range recited in instant claim 1. US 2004/0209366 A1 discloses that immunoliposomes of the invention were capable of delivery of liposome-encapsulated anti-cancer drug to target cells and at a higher efficiency than immunoliposomes that are prepared by incorporating an activated linker into the liposome prior to the attachment of the protein of interest to the liposome. US 2004/0209366 A1 further discloses that it is *optional* for a hydrophilic polymer such as PEG, PEG-PE or PEG-DSPE to be added to the lipid nucleic acid complex (see especially [0009]-[0010], [0012], [0015], [0019], [0036], [0137], [0150], [0165], Examples 5 and 7).

US 2004/0209366 A1 does not disclose wherein the scFv is directly conjugated to the cationic immunoliposome via a sulfur atom that was part of a SH group at the carboxy terminus of the scFv, including wherein the scFv is covalently bound to DOPE linked to MPB, nor wherein the scFv is capable of binding to a transferrin receptor.

Spragg *et al* teach preparing targeted liposomes of several types, such as cationic immunoliposomes or immunoliposomes sterically stabilized with PEG, including loaded with a cytotoxic agent, by modifying an antibody against a target with succinimidyl-S-acetylthioacetate (SATA), *i.e.,* by adding a sulfhydral group (*i.e.,* thiol) to an antibody. Spragg *et al* teach that the cationic liposomes are comprised of MBP-PE, DOPE, DOTAP and DOPC. Spragg *et al* teach that the sterically stabilized liposome containing PEG may have sterically hindered antibody-mediated binding to the target molecule since binding was lower than classical immunoliposome binding (especially page 8796 at column 1 and column 2 under "Liposome Preparation" and "Antibody Conjugation" and page 8799 at column 2 first full paragraph).

Martin *et al* teach irreversible coupling of immunoglobulin Fab' fragments to liposomes using direct coupling via a sulfur atom on the Fab' and using MPB. Martin *et al* further teach that their method provides improved coupling efficiencies and leads to the formation of a stable antibody-vesicle linkage. Martin *et al* teach that it should be possible to link any thiol-containing protein ligand to MPB-PE containing liposomes, that coupling via the thiol group on the Fab' fragment results in favorable orientation on the vesicle surface. Martin *et al* teach the absence of the Fc region of the antibody is desirable to eliminate the possibility of Fc-mediated binding and complement activation. Martin *et al* also teach cytoplasmic delivery of liposomal contents (see entire article, for example, abstract, page 286 at column 2 at the third full paragraph, Results, and Discussion).

US 4,946,778 discloses that use of single chain antibodies such as scFv has advantages over use of conventional antibodies or Fab' fragments of conventional antibodies, such advantages being smaller size, greater stability, significantly reduced cost, reduced immunological reaction, and thus increased safety and efficacy for therapeutic applications, and that they can more easily be engineered to improve binding affinity and specificity. US 4,946,778 discloses that all of the uses that the prior art has envisioned for monoclonal or polyclonal antibodies, or for the variable region fragments thereof, can be considered for the molecules of the present invention, *i.e.,* single chain Fv fragments (scFv) (especially column 2 at lines 22-35 and column 3 at ines 29-48).

Wang *et al* teach generating an scFv with anti-CD19 specificity with a carboxy terminal cysteine, *i.e.,* contains a sulfhydral group, for the purpose of covalently linking the scFv-Cys with a toxin through a disulfide bond, and using the scFv linked to the toxin to effectively target the toxin to CD19-expressing B cell lymphomas and leukemias and that the disulfide bond did not interfere with the antigen binding activity of scFv. Wang *et al* teach that advantages of using scFv rather than intact antibody is smaller size for better tumor tissue penetration (especially abstract, page 1 at the first two paragraphs, paragraph spanning pages 882 and 883, and first sentence of the last paragraph on page 883).

Xu *et al* teach transferrin-cationic liposomes mixed with DNA encoding wild type p53. Xu et al teach use of the nucleic acid transferrin-cationic liposomes are effective for transfection of tumor cells, administration results in significant inhibition of tumor growth and prevents relapse and metastasis of mammary tumors in nude mice, and for treatment of head and neck cancer.

U.S. 6,200,956 B1 discloses immunoliposomes, including cationic polymers of cationic lipids chemically coupled, covalently or non-covalently, to a ligand of a membrane receptor present at the surface of a target cell type, such as a tumor cell and further comprising DNA that is to be delivered to the said target cell type, *i.e.,* is a nucleic acid-cationic immunoliposome complex, and pharmaceutical compositions thereof. US 6,200,956 B1 further discloses that transferrin and antibodies/fragments of antibodies are ligands of the target cell surface molecule transferrin, *i.e.,* are targeting molecules for cells such as tumor cells, and further discloses pharmaceutical compositions are targeting molecules for cells such as tumor cells (especially column 1 at lines 63-67, column 2 at lines 1-15 and 26-33 and column 4 at lines 20-64).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a targeted immunoliposome such as the one disclosed by US 2004/0209366 A1 that comprises scFv loaded with an effector molecule such as a nucleic acid molecule encoding tumor suppressor gene p53, such as the DNA encoding wild type p53 taught by Xu *et al* in their targeted cationic liposome, but that has scFv *directly* conjugated to the liposome, similar to that of the Fab' conjugated directly to the liposome taught by Martin *et al*, by coupling the scFv disclosed by US 2004/0209366 A1 to Cys as taught by Wang *et al* and mixing the scFv at the ratio disclosed by US 2004/0209366 A1 with a cationic liposome such as taught by Spragg *et al* and Martin *et al* that contains MPB-PE, rather than using a linker with a Cys-reactive maleimide-PEG-DSPE to attach the antibody as disclosed by US 2004/0209366 A1, and to have mixed the cationic immunoliposome with nucleic acid encoding wild type p53 at the ratio disclosed by US 2004/0209366 A1, to produce a targeted cationic immunoliposome such as that disclosed by US 6,200,956 B1 that comprises a covalently conjugated antibody fragment that targets the transferrin receptor and contains a nucleic acid molecule. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an scFv with specificity for the transferrin receptor like the antibodies with anti-transferrin receptor specificity disclosed by U.S. Patent No. 6,200,956 B1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat cancer of the head and neck more effectively using a non-sterically stabilized cationic immunoliposome because: (1) U.S. Patent No. 6,200,956 B1 discloses using scFv or Fab' antibody fragments linked to effector cationic lipid nucleic acid complexes provides the ability to conveniently customize the complex for delivery to specific cells and tissues such as tumor cells, (2) Xu *et al* teach using a transferrin-targeted immunoliposome with the effector molecule wild-type p53 is useful for treatment of head and neck cancer, (3) Wang *et al* teach that it is advantageous to use scFv rather than intact antibody because the smaller size is better for tumor tissue penetration and that an scFv-Cys with specificity for a tumor cell antigen could be linked to a toxin through the sulfur atom on the Cys without loss of antigen binding activity to the B cell lymphomas and leukemias and used for tumor targeting, (4) Martin *et al* teach

that it is advantageous to use antibody fragments that do not contain the Fc region, *i.e.*, such as Fab' (or scFv) in order to eliminate the possibility of complement activation, (5) U.S. Patent No. 6,200,956 B1 discloses that transferrin and anti-transferrin receptor antibodies or antigen binding fragments thereof are ligands of the target cell surface transferrin receptor, (6) US 2004/0209366 A1 discloses that nucleic acid encoding p53 is an effector for cancer cells, (7) Martin *et al* teach irreversible and superior coupling efficiency of Fab' fragments to liposomes via direct conjugation via a sulfur atom on the Fab' using MPB, and that it should be possible to link any thiol-containing protein ligand to MPB-PE- containing liposomes because coupling via the thiol group results in favorable orientation on the vesicle surface, (7) Spragg *et al* teach cationic immunoliposomes containing MBP-PE, DOPE, DOTAP and DOPC, and further teach that sterically stabilized immunoliposomes contaiing PEG may have sterically hindered antibody mediated binding to the target molecule since binding was lower than classical immunoliposome binding, (8) the scFv fragments disclosed/taught by U.S. Patent No. 6,200,956 B1 and Wang *et al*, have the art taught advantage of being more effective for penetrating tumor tissue, and (9) US 4,946,778 discloses the advantages of using scFv antibody fragments, and that they may be used for any application antibodies or other variable region antibody fragments are used for.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 3/30/06 on pages 7-22.

It is the Examiner's position with regard to Applicants arguments to US 2004/0209366 A1 (at pages 17-22 of Applicant's said amendment), that the disclosure in Example 7 is a ratio of scFv antibody fragment to lipid of 15.6 ug: 1 u mol lipid which is within the ratio range required in base claim 1 because the liposome used in Example 7 is made of the same constituents as the liposome of Example 6 wherein 1 umol of the lipid equals 0.21 mg or 210 ug, and is not made of the exemplary liposome discussed by Applicant on page 13 of Applicant's amendment wherein 1 umol lipid equals 0.58 mg. It is the Examiner's further position that the remainder of the references are being argued separately or the arguments are moot in light of this new rejection.

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
May 30, 2006

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600